I. AMENDMENT

In the Specification:

On page 135, line 30, please replace "FIG. 3" with --FIG. 4A--.

In the Claims:

Please cancel claims 47-52, 59, 63, 65-67, and 81-90, without prejudice or disclaimer.

Please amend the following claim:

103. (Amended) A process of isolating a substance with an ability to act as a specific agonist of a kappa opioid receptor, said process comprising the steps of:

a) providing an opioid receptor polypeptide comprising a second extracellular loop and encoded for by a nucleic acid sequence comprising at least 30 contiguous bases of SEQ ID NO:1;

b) contacting said opioid receptor polypeptide with a composition comprising said substance;

c) detecting the ability of said substance to interact as an agonist with said opioid receptor; and

d) isolating said substance if the ability of said substance to specifically interact with the opioid receptor is detected.

Please add the following claims.

--115. A process of screening a substance for its ability to interact with an opioid receptor comprising:

a) expressing either (1) a recombinant opioid receptor polypeptide encoded for by a nucleic acid sequence comprising at least 30 contiguous bases of SEQ ID NO:1 or (2) a recombinant opioid receptor polypeptide comprising the second extracellular loop and encoded for by a nucleic acid sequence comprising at least 30 contiguous bases of SEQ ID NO:11;

b) contacting said substance with the opioid receptor polypeptide; and

c) detecting the ability of said substance to interact with said opioid receptor polypeptide.

116. The process according to claim 115, wherein said opioid receptor polypeptide is a chimeric opioid receptor polypeptide.

117. The process of claim 116, wherein one polypeptide of the chimeric opioid receptor polypeptide comprises the second extracellular loop of kappa opioid receptor.

118. The process of claim 116, wherein one polypeptide of the chimeric opioid receptor polypeptide comprises the third extracellular loop of kappa opioid receptor.

119. The process of claim 116, wherein the chimeric opioid receptor polypeptide comprises polypeptide portions of both kappa and delta opioid receptors.

120. The process according to claim 116, wherein the chimeric opioid receptor polypeptide comprises $\kappa_{1\text{-}78}/\delta_{70\text{-}372}$ or $\delta_{1\text{-}69}/\kappa_{79\text{-}380}$.

121. The process according to claim 115, wherein the opioid receptor polypeptide is a kappa opioid receptor polypeptide having the sequence of SEQ ID NO:2 or SEQ ID NO:12.

122. The process of claim 121, wherein said opioid receptor polypeptide is a kappa opioid receptor polypeptide encoded for by the polynucleotide of SEQ ID NO: 1.

123. The process of claim 121, wherein said opioid receptor polypeptide is a kappa opioid receptor polypeptide encoded for by the polynucleotide of SEQ ID NO: 11.

124. A process of isolating a substance with an ability to act as a agonist of a kappa opioid receptor comprising:

a) providing a recombinant opioid receptor polypeptide that includes the second extracellular loop and that is encoded for by a nucleic acid sequence comprising at least 30 contiguous bases of SEQ ID NO:1 or SEQ ID NO:11;

b) contacting said opioid receptor polypeptide with a composition comprising the substance;

c) detecting the ability of the substance to interact as an agonist with the opioid receptor polypeptide; and

d) isolating the substance if an ability of the substance to interact with the opioid receptor polypeptide is detected.

125. The process of claim 124, wherein the opioid receptor polypeptide is a chimeric opioid receptor polypeptide.

126. The process of claim 124, wherein one polypeptide of the chimeric opioid receptor polypeptide comprises the third extracellular loop of delta opioid receptor.

127. The process of claim 124, wherein the opioid receptor polypeptide comprises portions of both kappa and delta opioid receptors.

128. The process of claim 124, wherein the chimeric polypeptide comprises $\kappa_{1\text{-}78}/\delta_{70\text{-}372}$ or $\delta_{1\text{-}69}/\kappa_{79\text{-}380}$.

129. A process of screening a substance for its ability to act as an agonist of a kappa opioid receptor comprising:

a) expressing either (1) a chimeric recombinant opioid receptor polypeptide encoded for by a nucleic acid sequence comprising at least 30 contiguous bases of SEQ ID

NO:1 or (2) a chimeric recombinant opioid receptor polypeptide comprising the second extracellular loop and encoded for by a nucleic acid sequence comprising at least 30 contiguous bases of SEQ ID NO:11;

b) contacting said substance with the opioid receptor polypeptide; and

c) detecting the ability of the substance to interact as an agonist with the opioid receptor polypeptide.

130. The process of claim 129, wherein said nucleic acid sequence comprises at least 40 contiguous bases of SEQ ID NO:1.

131. The process of claim 129, wherein said nucleic acid sequence comprises at least 55 contiguous bases of SEQ ID NO:1.

132. The process of claim 129, wherein said nucleic acid sequence comprises at least 70 contiguous bases of SEQ ID NO:1.

133. The process of claim 129, wherein one polypeptide of the chimeric opioid receptor polypeptide comprises the second extracellular loop of kappa opioid receptor.

134. The process of claim 129, wherein one polypeptide of the chimeric opioid receptor polypeptide comprises the third extracellular loop of kappa opioid receptor.

135. The process of claim 129, wherein the chimeric opioid receptor polypeptide comprises polypeptide portions of both kappa and delta opioid receptors.

136. The process of claim 97, wherein the recombinant opioid receptor polypeptide comprises the second extracellular loop.

II. RESPONSE TO OFFICE ACTION

A. Status of the Claims

The Office Action dated August 10, 2000 rejects claims 47-52, 59, 63-67, 83, 84, 86-88, 90, 97, and 103-114. Herein, claims 47-52, 59, 63, 65-67, and 81-90 are cancelled, claim 103 is amended, and claims 115-136 are added. Support for the added claims can be generally found in the cancelled claims and in the Specification at least on page 96 and on page 167. The Specification was amended on page 135 to refer to the appropriate figure that contains the sequence alignment; instead of referring to FIG. 3 on line 30, the Specification has been amended to refer to FIG. 4A. Earlier on the same page at line 16, the correct figure is said to contain the sequence comparison between the mouse and human polypeptide sequences. Applicants contend that no new matter has been added to the Specification. Claims 91-136 are the subject of this response. A copy of the claims is provided in Appendix A.

B. Claims 47-52, 59, 63-67, 83, 84, 86, 88, 90, 97-102, and 109-114 Have Utility

Claims 47-52, 59, 63-67, 83, 84, 86, 88, 90, 97-102, and 109-114 were rejected under 35 U.S.C. § 101 as not being supported by a specific, substantial, and credible asserted utility or a well-established utility. The Action alleges that the specification provides a description of a "partially isolated protein," but does not disclose its biological role or its significance. It further contends that there is no immediately obvious patentable use for the protein in the absence of knowledge about its natural ligands or biological significance. Finally, the Action states, "To employ a protein of the instant invention in the identification of substances which bind to and/or mediate activity of the said receptor is clearly to use it as the object of further research which has not been determined by the courts to be a non-patentable utility." Applicants respectfully traverse this rejection.

Applicants vehemently dispute that the "instant application does not disclose the biological role of this protein or its significance." Applicants emphasize that the amino acid sequence of SEQ ID NO:12 is human kappa opioid receptor sequence. The Specification clearly discloses this fact. *See, e.g.,* Specification at page 135, lines 12-15; page 30, line 34-page 31, line 1; and, page 11, lines 34-35. The biological role and significance of an opioid receptor subtype cannot be disputed and is amply described in the Specification. Indeed, pages 3-8 of the disclosure are devoted to discussing opioid drugs and opioid receptors. Applicants contend that the general subject matter of the invention has well-established importance.

Furthermore, Applicants point out that it is the claim that must be evaluated for compliance with the utility requirement. MPEP 2107.01. The claims are directed to process of "screening a substance for its ability to interact with an opioid receptor" and "isolating a substance for an ability to act as an agonist of a kappa opioid receptor." The Specification discusses the usefulness for such processes, the problems experienced by existing methods, and the improvements to those methods as a result of the invention. Specification at least at pages 9, line 29-page 11, line 9. For example, the implementation of cloned opioid receptor polypeptides in an assay system allows a person skilled in the art to draw conclusions with respect to the particular opioid receptor subtype used. Previously, subtype specificity was difficult to assess since the subtype could not be identified using a non-recombinant system in which the cell expressed several subtypes. As the disclosure discusses, subtype specificity is important for identifying pharmaceutical compositions to produce desired physiological effects related to opioid receptor activity. Therefore, a case for both an asserted utility and a well-established utility for the claimed invention has been made.

The Action contends that there is no actual or specific significance attributable to the protein identified in the specification. It further alleges, "To employ a protein of the instant invention in the identification of substances which bind to and/or mediate activity of the said receptor is clearly to use it as the object of further research which has been determined by the courts to be a non-patentable utility." Applicants do not agree.

The present situation is not analogous to *Brenner v. Manson*, 383 U.S. 519, 148 U.S.P.Q. 689 (1996). As discussed above, the general subject matter of the invention—kappa opioid receptors—are a class of proteins whose physiological importance is well documented. In *Brenner*, a class of compounds was the subject matter of the invention, and the only distinction of this class was that it was structurally similar to other compounds that were being studied as anti-tumor agents. *Id.* at 690. The situations are simply not analogous because SEQ ID NO:12 is a kappa opioid receptor sequence, and kappa opioid receptors are clearly molecules whose importance is not in question.

Moreover, the Specification points out the degree of identity between the mouse kappa opioid receptor polypeptide sequence and the human kappa opioid receptor polypeptide sequence. While the human sequence lacks the first 87 amino acids of the protein, it has extensive *identity* with the mouse kappa opioid receptor. As shown in FIG. 4A,[1] of the 290 amino acids identified from the human sequence that line up with the mouse sequence, 273 of the residues are identical to the corresponding residue in the mouse sequence, and all of the remaining residues except for one (amino acid 358) would be recognized by one of skill in the art to be similar to the cognate mouse residue.

[1] On page 135 in the Specification, this figure is identified as "Figure 3" (line 30), instead of FIG. 4A. The Specification is being amended to reflect this.

A variety of experiments were done using a nucleic acid sequence encoding a mouse kappa opioid receptor. For example, binding studies were done (Specification at p. 124) to confirm that the clone obtained from mice was indeed the kappa opioid receptor (Specification at p. 125). Furthermore, the binding potencies of known opioid ligands were evaluated using the mouse kappa opioid receptor. (Specification at p. 126; p. 142-143). Experiments were also done using chimeric receptors. Some of these constructs contained a kappa opioid receptor polypeptide sequence missing the first 78 residues, and these constructs exhibited κ-selective agonist binding; these constructs lacking the N-terminus of the protein behaved like the full-length clone. With respect to the kappa portion of the construct, it is only nine amino acids longer than SEQ ID NO:12, the human kappa opioid receptor sequence. Moreover, SEQ ID NO:12 contains a second extracellular loop that is identical to the second extracellular loop described in the Specification as being involved in agonist binding. Specification at least at page 96, line 7; pages 165-170. The human sequence is tantamount to the sequence of the truncated constructs, and a person of ordinary skill in the art would appreciate this. Considering the extensive identity between the mouse and human kappa opioid receptor polypeptide sequences and the extensive characterization of the mouse kappa opioid receptor polypeptide, including the use of partial kappa opioid receptor sequences, one of ordinary skill in the art would understand that the instant disclosure provides actual and specific significance for the human kappa opioid receptor sequence of SEQ ID NO:12.

Moreover, Applicants submit that a proper *prima facie* rejection has not been made by the examiner. "Only after the PTO provides evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility does the burden shift to the applicant to provide rebuttal evidence sufficient to convince such a person of the invention's asserted utility." *In re*

Brana, 51 F.3d 1560, 34 U.S.P.Q. 2d 1436, 1443 (Fed. Cir. 1995). Given that Applicants have identified the sequence as human kappa opioid receptor sequence, Applicants contend that the PTO has presented no evidence showing why a person would doubt the asserted utility of the present invention.

For these reasons, Applicants contend that the rejection of these claims as lacking utility is inappropriate and respectfully request that this rejection be withdrawn.

C. Specification Adequately Supports Claims 47-81, 83, 84, 88, 90, 97-102, and 109-114

The Office Action objected to the specification and rejected claims 47-81, 83, 84, 88, 90, 97-102, and 109-114 under 35 U.S.C. § 112, first paragraph, as failing to adequately teach how to use the instant invention because the claimed invention is not supported by a specific, substantial, and credible asserted utility or a well-established utility. Applicants respectfully traverse this rejection.

This rejection was set forth in the Action under the heading entitled "Claim Rejections - 35 USC § 112, first paragraph - lack of written description" and under the subheading "A." Because of the emphasis on utility, Applicants has addressed this rejection on the grounds of enablement, not written description. If this is an incorrect understanding of the rejection, Applicants' representative would appreciate being notified by the Examiner so the rejection can be properly addressed.

Satisfaction of the enablement requirement of 35 U.S.C. § 112, first paragraph requires that the specification teach "those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" *In re Wright*, 999 F.2d 1557, 1561, 27 U.S.P.Q.2d 1510, 1513 (Fed. Cir. 1993). The claims are directed to processes of screening and

isolating substances that interact with an opioid receptor. The Specification discloses SEQ ID NO:11 and SEQ ID NO:12. It also teaches how to make and use these kappa opioid receptor sequences, and it shows how the mouse homologs can be used in such screening methods. *See, e.g.,* Specification text accompanying Table 3 on pages 141-143. As discussed above, the mouse and human sequences exhibit significant identity over a large part of the protein. Applicants repeat the arguments made with respect to utility and contend that the since the claimed invention has utility, it is also enabled. Consequently, Applicants respectfully request the withdrawal of this rejection.

E. Claims 47, 59, 84, 97, and 109 Satisfy § 112, first paragraph

Under subheading "B," claims 47, 59, 84, 97, and 109 were rejected under 35 U.S.C. § 112, first paragraph because SEQ ID NO:11 is a partial genomic sequence. Applicant is unsure as to whether the basis for this rejection is enablement or written description, particularly in light of the suggestion of how the claims should be amended. Therefore, Applicants address both grounds.

Insofar as the claims are enabled, Applicants adhere to the arguments made in the previous response. To summarize, Applicants contend that 1) the Specification provides sufficient guidance and numerous working examples of less than full-length opioid receptors, for example, $\kappa_{1\text{-}74}/\delta_{65\text{-}372}$, $\kappa_{1\text{-}78}/\delta_{70\text{-}372}$, $\delta_{1\text{-}69}/\kappa_{79\text{-}380}$, $\kappa_{1\text{-}74}/\delta_{75\text{-}380}$; 2) the Specification indicates which portion of the nucleic acid sequence is coding sequence; and 3) the cited references are not relevant as they clearly are distinguishable from the situation involving the present invention.

Applicants note that the Action's comment about what the reference George *et al.* states does not indicate the reference's support for the Examiner's position. Even if only "possible" relationships between biomolecules can be identified, this reference cannot be taken to mean that

undue experimentation is required to practice the claimed invention since the reference itself identifies that similarity between molecules (in this case, between the mouse and human polypeptides) is relevant. The Examiner has relied on this article to support his position that undue experimentation would be required since alteration of amino acid sequence could have an effect on a protein's folding. However, Applicants contend not only does the reference fail to support that position, but also it makes Applicants' point. Thus, simply because a reference may not be as strong for the Applicants' position does not mean it consequently strengthens the Examiner's argument.

As for the Examiner's comment about the Cunningham and Wells reference, Applicants contend that this reference cannot be taken to mean that undue experimentation is required to use a human kappa opioid receptor polypeptide in the claimed screening methods. Even if the reference reports that single amino acid changes in the growth hormone receptor could affect its binding activity, there is 1) no indication that this would apply to the kappa opioid receptor and 2) no indication that binding would be so altered that the screening processes of the claimed invention *would not work*. The art at the time the application was filed is replete with examples of chimeric proteins, involving a wide variety of proteins; in many instances, these chimeric proteins have been created and evaluated as possessing activity and specificity comparable to its full-length counterpart. Swapping of polypeptide segments is well known in the area of receptors. Furthermore, as demonstrated by the examples, chimeric proteins comprising portions of the mouse kappa opioid receptor had binding activity for agonists and antagonists, depending upon which portion of the receptor was employed in the chimera.

For the reasons argued above and in the previous response, Applicants contend that the claimed invention is fully enabled by the Specification.

With respect to a rejection based on written description, Applicants point out that the claimed of the present invention are directed to processes. The Guidelines for the Written Description Requirement do not address the present situation. The examples in the Guidelines are not drawn to processes involving a partial sequence. Applicants contend the present claims satisfy the written description requirement as the application describes processes involving all or part of SEQ ID NO:11, which includes the second extracellular loop. The second extracellular loop is a limitation of the claims involving a kappa opioid receptor based on SEQ ID NO:11. The second extracellular loop identified in the mouse protein sequence is identical the corresponding amino acid sequence in the human kappa opioid receptor, which is disclosed in the application. Applicants contend that the written description has been satisfied with respect to the claims.

F. Claims 59, 63, 65-67, and 103-114 Satisfy § 112, first paragraph

The rejection of claims 59, 63, 65-67, and 103-114 was maintained under 35 U.S.C. § 112, first paragraph. Independent claims 59 and 103 have been amended (or cancelled and rewritten as a new claim) to clarify further the invention. These claims recite an opioid receptor polypeptide comprising the "second extracellular loop." Applicants contend the claims as amended satisfy 35 U.S.C. § 112, first paragraph, and respectfully request this rejection be withdrawn.

G. Claims 59, 63, 65-67, and 103-114 Satisfy § 112, second paragraph

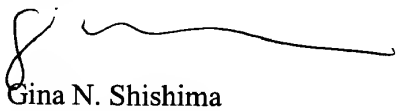
The Action rejects claims 59, 63, 65-67, and 103-114 as being indefinite under 35 U.S.C. § 112, first paragraph. It alleges that the claims do not make it clear whether an agonist or an antagonist is binding the receptor. Applicants respectfully traverse this rejection.

Applicants note that the rejected claims (and the added claims that correspond to rejected claims) recite "detecting the ability of [the] substance to interact *as an agonist* with [the] opioid receptor polypeptide." (Emphasis added.) Applicants contend that this step addresses the concern expressed in the Action. It is clear that agonist binding, not antagonist binding, is distinguished by the steps of the claim. Therefore, Applicants respectfully request the withdrawal of this rejection.

H. Conclusion

Applicants note that no rejections have been lodged against claims 91-96 and submit these claims are allowable. With respect to the outstanding rejections, Applicants believe that the present document is a full and complete response to the referenced Official Action. In conclusion, Applicants submit that, in light of the foregoing remarks, the present case is in condition for allowance and such favorable Action is respectfully requested. Should the Examiner have any further questions or comments, or believe that certain clarifications might more readily progress the present application to issuance, a telephone call to the undersigned Applicants' representative at (512) 418-3081 is earnestly solicited.

Respectfully submitted,



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